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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/153,133	09/15/1998	D. DUKE LEE	04712/018002	5068

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EXAMINER
SHARAREH, SHAHNAM J

ART UNIT	PAPER NUMBER
1617	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/153,133	Applicant(s) LEE ET AL.	
	Examiner Shahnam Sharareh	Art Unit 1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Peri d for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 5/6/2002 .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-3,5,6,8-19,21-31 and 33-42 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-3,5,6,8-19,21-31 and 33-42 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Continued Examin tion Und r 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on June 6, 2002 has been entered.

Status of the Claims

Claims 1-3, 5-6, 8-19, 21-31, 33-42 are pending.

Priority

Priority of the instant application as set fort in Paper No. 6 is September 15, 1998.

Response to Amendment

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Any rejection that is not addressed in this Office Action is considered obviated in view of the amendment and arguments.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-6, 8-12, 15-25 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-11 of U.S. Patent No. 6,214,368. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are directed to compositions comprising amorphous calcium phosphate and a second calcium phosphate source for in vivo use. Accordingly, the scope of the claims overlap.

In the instant case, the patented claims are directed to formable paste composition comprising at least 90% calcium phosphate material and a second calcium phosphate material (see claim 1). The instant claims differ in the amounts of the amorphous calcium phosphate contained within the composition. However, modification of amounts can be achieve by routine experimentation, and the ordinary skill in the art would have had a reasonable expectation to observe beneficial clinical effects of calcium phosphate when administered in vivo.

Claim Rejections - 35 USC § 112

Claims 6, 15-19, 21-25, 26-27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 15 and all dependent claims thereof are directed to the limitation "a second calcium phosphate" which renders the claim as a whole vague. Applicant is suggested to clarify to which calcium phosphate is applicant referring? There is no recitation of first calcium phosphate. Specifically, what is considered as the second calcium phosphate in relative to the amorphous calcium phosphate? How are they different? Is the second calcium phosphate of a different source, positioned in a different part within the composition, and separate from the first calcium source? For example, if the second calcium phosphate source is amorphous calcium phosphate, how is the first calcium phosphate source different from the second. Accordingly, the metes and bounds of the claim is not clear.

The term "strongly" in claim 6 and 19 is a relative term which renders the claim indefinite. The term "strongly" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 1-6, 8, 15-19, 21, 28-31, 40-41 are rejected under 35 U.S.C. 102(b) as being anticipated by Constantz US Patent 5,782,971 (Constantz).

The instant claims are directed to injectable paste compositions comprising calcium phosphate having a solid content of greater than or equal to 40 wt%. Applicant is also informed that a recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. *In re Casey*, 152 USPQ 235 (CCPA 1967).

Constantz disclose injectable paste compositions comprising amorphous calcium phosphate mixtures in combination with a second calcium source such a tetra calcium phosphate in amounts higher than 40 wt% (see abstract, col 4, lines 1-60; col 5, lines 1-10). The calcium phosphate containing compositions moieties of Constantz are flowable and injectable and are able to be combined with various proteins (see col 5, lines 60-66; col 6, lines 34-45, line 60-63). Thus, Constantz anticipates the limitations of the instant claims.

Claims 1-6, 8, 15-19, 21, 28-31, 28, 40-41 are rejected under 35 U.S.C. 102(e) as being anticipated by Poser et al US Patent 5,968,253 (Poser).

Poser discloses paste-like flowable compositions comprising 60-95% tricalcium phosphate, a second calcium phosphate source such as monocaclium phosphate monohydrate, and an aqueous injectable lubricant (see abstract, col 6, lines 48-67; col 13, lines 19-51). Thus, Poser anticipates the limitations of the instant claims

Claim Rejections - 35 USC § 103

Claims 1-3, 5-6, 8, 10-19, 21, 23-31, 40-41are rejected under 35 U.S.C. C. 103(a) as being unpatentable over Reyveld US Patent 4, 016,252, in view of Amerongen et al US Patent 5,443,832 and Constantz et al US Patent 5,782,971.

The instant claims are directed to adjuvant compositions comprising amorphous calcium phosphate, and methods of using thereof.

Relyveld teaches methods of improving vaccine formulations by using calcium phosphate gels (an amorphous formulation) as an adjuvant wherein the calcium to phosphate ratio is from 1.62 to 1.85 (col 2 lines 1-15). Reyveld fails to show the instant 40 wt % solids in his compositions.

Amerongen is used to show that calcium phosphate particles (hydroxy appetite) is used in amounts of higher than 40% to elicit an immune response in mammals. Amerongen teaches 1mg of HA in 200 μl of PBS (example 2). Amerongen fails to teach their compositions in an injectable paste form.

Constantz et al teach amorphous calcium phosphate containing compositions as a suitable drug delivery vehicle (col 2, lines 60-67; col 6, lines 61-63). Constantz specifically teach paste formulations of calcium phosphate that are capable of hardening after administration (col 6, lines 40-50). Constantz's composition comprises about 15 wt% of the dry ingredient (solid component) having particle sizes of about o.5-100 microns (col 5 lines 1-3; and lines 14-25). Constantz further indicates that one of ordinary skill in the art would be able to modify the viscosity of his composition by varying the percentages of solids in his composition, thus allowing for ease of administration (col 6, lines 32-39). Constantz also teaches that such composition can carry a suitable protein and be used as a drug delivery system (see col 5, lines 61-65 and col 6, line 62). Constantz, however, fails to disclose vaccine formulations.

All cited art teach various methods of using calcium phosphate particles suitable in drug delivery systems, therefore, their teachings are viewed to be analogous.

It has been established that the prior art can be modified or combined to reject claims as prima facia obvious as long as there is a reasonable expectation of success. Accordingly, it would have been obvious to one of ordinary skill in the art at the time of invention to modify concentrations of Relyveld calcium phosphate adjuvant composition to contain about 40 wt % solid component by routine experimentation to formulate a hardenable calcium phosphate formulation, because as shown by Amerongen and Constantz, such compositions are easily administered to a site of interest for the intended clinical utility.

Claims 9, 22, 28-31, 33, 34-38, 42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Relyveld US Patent 4, 016,252, in view of Amerongen et al US Patent 5,443,832 and Constantz et al US Patent 5,782,971, as applied to claims 1-3, 5-6, 8, 10-19, 21, 23-31, 40-41 above, and further in view of and Gupta et al (Vaccine Design, Chapter 8 pp 229-248, 1995), or Kossovsky et al US Patent 5,462,751.

The instant claims are directed to adjuvant compositions comprising calcium phosphate and a second adjuvant.

The teachings of Relyveld, Amerongen and Constantz are discussed above.

Gupta is used to show that combination of adjuvants, such as aluminum adjuvants, are readily used in the art to complement their activities and thus enhance the potency of vaccine formulations (see page 241, sec 4). Gupta teaches that the potency of vaccine formulations can be increased by incorporation of other adjuvant-active components (page 241, last paragraph). Moreover Gupta teaches the use of calcium phosphate products in vaccines, as well as, the role of the precursor concentration of reactants in forming suitable calcium phosphate compositions as an immunologic adjuvant (page 238-239, sec 3.2; page 240). However, Gupta does not specifically teach various percentages of solid amounts, or the use of a cytokine.

Kossovsky et al teach compositions comprising calcium phosphate (brushite) compositions that are suitable for delivery in immune response eliciting moieties such as peptides and proteins (abstract, example 1-2). Kossovsky further teaches attaching a biologically active peptide or protein to his calcium phosphate compositions for delivery of such immunostimulatory complexes (examples 3-5). Peptides used in Kossovsky's

compositions can be selected from any immunologically pair members such as IgG, IgM etc..polycolonal or monoclonals specific to a cell surface antigen (col 5, lines 65-67;col 6, lines 1-10). Kossovsky also teaches coating of his core complex by using a second type component such as Cellobiose (a natural polymer) to enhance specificity of his formulations (abstract, example 2). Kossovsky, however, fails to specifically teach a hardenable paste formulation for injection.

Nevertheless, it would have been obvious to one of ordinary skill in the art at the time of invention to modify concentrations of Relyveld calcium phosphate adjuvant composition to contain about 40 wt % solid component by routine experimentation, as discussed above, and further incorporate a second adjuvant, separately, as taught by Gupta; or in the form of a coating, as taught by Kossovsky, to enhance the potency and the therapeutic efficacy of Relyveld's vaccine. Such modifications are routine in the art and the ordinary skill in the art would have had a reasonable expectation of success in observing enhanced activity of Relyveld's vaccine.

Response to Arguments

Applicant's arguments filed June 06, 2002 have been fully considered but they are not persuasive.

With respect to the rejection of claims under 35 U.S.C. 103(a) as being unpatentable over Relyveld US Patent 4, 016,252, in view of Amerongen et al US Patent 5,443,832 and Constantz et al US Patent 5,782,971, as applied to claim 1-3, 5-6, 8, 10-14, 17-18, 23-27, 39, 43-44 above, and further in view of and Gupta et al

(Vaccine Design, Chapter 8 pp 229-248, 1995), or Kossovsky et al US Patent 5,462,751, Examiner maintains the rejection for the reasons set forth above.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In the instant case, Relyveld clearly sets forth the use and advantages of calcium phosphate as an immunogenic adjunct in vaccine preprations. Thus, such a utility is well recognized in the art. The secondary refrences, specially Constatnz, discusses the suitability of calcium phosphate compositions as a drug delivery system at higher concentrations. Thus, all elements of the claimed inventions are taught by the cited references and combination of such teachings establishes *prima facia* obviousness of the instant claims over the cited prior art.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, again, the use of calcium phosphate as an immunogen is well recognized and available to the ordinary skill in the art. Constantz teaches an improvement of local drug delivery systems when

a calcium phosphate system is used at higher concentrations. The teachings of Gupta and Kossovsky further supplement such knowledge. Thus, combining the teachings of cited prior art to enhance the activity of Relyveld's vaccine would have been expected.

Conclusion

No claims are allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure: Constantz US Patent 5,952,010.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shahnam Sharareh, PharmD whose telephone number is 703-306-5400. The examiner can normally be reached on 8:30 am - 6:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's Acting Supervisor, Russell Travers, can be reached on 703-308-4603. The fax phone number for this Group is 703-308-4556. Any inquiry of a general nature of relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is 703-308-1235.

RUSSELL TRAVERS
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